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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte
GARY VAN NEST, STEPHEN TUCK, and JOSEPH EIDEN, JR.

Appeal 2008-2932
Application 09/642,492
Technology Center 1600

Decided: July 23, 2008

Before DEMETRA J. MILLS, LORA M. GREEN, and
FRANCISCO C. PRATS, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal[1] under 35 U.S.C. § 134 from the Examiner's final rejection of claims 1, 13-23, 25-33, and 37-42.[2] We have

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[1] This Appeal was heard on July 8, 2008.
[2] Claims 43-52 are also pending, but stand withdrawn from consideration (App. Br. 3).

jurisdiction under 35 U.S.C. § 6(b). Claim 1, 37, and 40 are the independent claims on appeal, and read as follows:

1. A method of modulating an immune response to a second antigen in an individual, comprising co-administering to the individual
(i) a complex comprising an immunomodulatory polynucleotide covalently conjugated to a first antigen and
(ii) a second antigen
wherein the polynucleotide comprises an immunostimulatory sequence (ISS), wherein the ISS comprises the sequence 5′-cytosine,guanine-3′, wherein the complex and the second antigen are administered at the same site in the individual and wherein the complex is administered in an amount sufficient to modulate an immune response in the individual to the second antigen.

37. A composition comprising
(i) a complex comprising an immunomodulatory polynucleotide covalently conjugated to a first antigen and
(ii) a second antigen,
wherein the polynucleotide comprises an immunostimulatory sequence (ISS), wherein the ISS comprises the sequence 5′-cytosine, guanine-3′, and wherein the first antigen is a viral conserved polypeptide and the second antigen is a viral variable polypeptide.

40. A composition comprising
(i) a complex comprising an immunomodulatory polynucleotide covalently conjugated to a first antigen and
(ii) a second antigen,
wherein the polynucleotide comprises an immunostimulatory sequence (ISS), wherein the ISS comprises the sequence 5′-cytosine, guanine-3′, and wherein the first antigen is an allergen.

The Examiner relies on the following references:

Anderson	US 4,673,574	June 16, 1987
Carlson	WO 98/16247	April 23, 1998
Schwartz	WO 98/55495	Dec. 10, 1998

Chu, *CpG Oligodeoxynucleotides Act as Adjuvants that Switch on T Helper 1 (Th1) Immunity*, 186 J. EXP. MED. 1623-1631 (1997).

Durali, *Cross-Reactions between the Cytotoxic T-Lymphocyte Responses of Human Immunodeficiency Virus-Infected African and European Patients*, 72 J. OF VIROLOGY 3547-3553 (1998).

Horner, *Immunostimulatory DNA Is A Potent Mucosal Adjuvant*, 190 CELLULAR IMMUNOLOGY 77-82 (1998).

Lee., *Control of immune responses by gene immunization*, 30 ANN. MED. 460-468 (1998).

We reverse.

BACKGROUND

According to the Specification, the "present invention provides methods which achieve modulation of an immune response against a second antigen, which is mediated by administration of a first antigen in conjunction with an immunostimulatory polynucleotide sequence." (Spec. 6.)

The Specification teaches that

> administration of a first antigen with an immunomodulatory polynucleotide comprising an immunostimulatory sequence(s) (ISS) elicits an immune response, particularly a Thl response, to a second antigen. Modulating the immune response to an additional antigen in response to administration of a first antigen offers distinct benefits and advantages. This immunotherapeutic approach obviates or at least reduces the need for having to design and manufacture various formulations reflecting different antigenic compositions. It also mitigates the requirement for identification of all relevant antigens for immunotherapy. For example, allergy desensitization therapy could be accomplished by administration of an ISS-containing polynucleotide and just one antigen. This is especially significant in some contexts, such as with cockroach, which contains many antigens. This may also be beneficial for relief from different allergens which, due to seasonal and

> geographical parameters, are encountered together. Further, with respect to immunization against pathogens (whether prophylactic or therapeutic) rapid mutations in antigenic proteins, such as coat proteins, would not necessitate identification of the changes and concomitant reformulation of vaccines to reflect the mutations. In the context of antigens administered in the form of antigen-carrier conjugates, such as oligosaccharide antigens, administration of one such conjugate with an ISS-containing polynucleotide would modulate the immune response to another antigen when administered with the same protein carrier. The immune response to the second antigen could be obtained without the need to generate additional formulations.

(*Id.* at 7-8.)

DISCUSSION

Claims 1, 13, 14, 17, 20-23, 25-33, 37, and 40-42 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Schwartz and Horner or Chu.

Schwartz is cited for teaching a "complex comprising an immunomodulatory polynucleotide comprising the sequence 5′-cytosine, guanine-3′" (CpG) conjugated to an antigen, such as an allergen (Ans. 5). Schwartz is also cited for teaching "antigens encompassing conserved and variable viral polypeptides and carrier molecules, and associating the antigen with carrier molecules." (*Id.*)

According to the Examiner:

> Schwartz et al. does not explicitly teach administering a second antigen with the complex. However, Schwartz et al. suggests that the immunomodulatory polynucleotide be administered with at least one, or more, antigens to modulate the immune response to the antigen. [Lines 9-15, page 12, in

> particular] The specific immune response that Schwartz et al. teaches is a Thl immune response. Therefore, administering multiple antigens with the immunomodulatory polynucleotide comprising the sequence 5'-cytosine,guanine-3' would have been prima facie obvious to one of ordinary skill in the art, at the time the invention was made. One of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation for inducing a Thl immune response to antigens administered with the immunomodulatory polynucleotide comprising the sequence 5'-cytosine,guanine-3' because Schwartz et al. teaches that the immunomodulatory polynucleotide is capable of inducing a Thl immune response to antigens administered with the immunomodulatory polynucleotide.

(Ans. 6.)

The Examiner cites Chu and Horner to support the rejection, relying on the references' teaching of the use of the 5'-cytosine,guanine-3' immunomodulatory polynucleotide as an adjuvant (Ans. 7). According to the Examiner, both Chu and Horner teach the ability of the polynucleotide to induce a Th1 response, thus, "the administration of a complex comprising immunomodulatory polynucleotide comprising the sequence 5'-cytosine, guanine-3' and at least one antigen would necessarily induce a Th1 immune response to all antigens." (*Id.*)

The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) secondary considerations of nonobviousness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). The Supreme Court has emphasized that "the [obviousness] analysis need not seek out precise teachings directed to the specific subject matter of the

challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007). However, an invention "composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *Id.* at 1741. "Often, it will be necessary . . . to look to interrelated teachings of multiple [references] . . . and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed[.]" *Id.* at 1740-41. "[T]his analysis should be made explicit" (*id.* at 1741), and it "can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" (*id.*).

Appellants argue that "Schwartz teaches an ISS-first antigen conjugate, but *does not teach administration of or modulation of an immune response to a second antigen*." (App. Br. 25.) Appellants argue further that Horner and Chu do not remedy the deficiency of Schwartz as neither reference "teaches or suggests modulating an immune response to a second antigen through co-administration of the second antigen and a complex comprising an immunomodulatory polynucleotide covalently conjugated to a first antigen." (*Id.* at 27.)

The portion of Schwartz relied upon by the Examiner states:

> In one embodiment, the invention provides compositions comprising ISS as the only immunologically active substance. . . .
>
> In other embodiments, ISS can be administered in conjunction with one or more members of the group of immunomodulatory molecules comprising antigens (including.

> but not limited to, proteins, glycoproteins, polysaccharides, and lipids), and/or immunomodulatory facilitators such as co-stimulatory molecules (including, but not limited to, cytokines, chemokines, targeting protein ligand, trans-activating factors, peptides, and peptides comprising a modified amino acid) and adjuvants (including, but not limited to, alum, lipid emulsions, and polylactide/polyglycolide microparticles). . . .
>
> The ISS and the antigen and/or immunomodulatory facilitator can be administered together in the form of a conjugate or co-administered in an admixture sufficiently close in time so as to modulate an immune response. Preferably, the ISS and immunomodulatory molecule are administered simultaneously. The term "co-administration" as used herein refers to the administration of at least two different substances sufficiently close in time to modulate an immune response. Preferably, co-administration refers to simultaneous administration of at least two different substances.

(Schwartz, p. 12 ll. 6-35.)

As noted by Appellants (App. Br. 26), the section of Schwartz relied upon by the Examiner discloses the administration of an ISS/antigen conjugate, or the administration of the ISS in admixture with one or more antigens, but does not teach or suggest administration of ISS/first antigen conjugate in admixture with a second antigen. At best, Schwartz teaches administration of an ISS/antigen conjugate in conjugation with an adjuvant (Schwartz Example 3, pp. 30-31). But the Examiner does not provide any evidence or scientific reasoning as why the ordinary artisan would have, based on the disclosure of Schwartz, administer an ISS/first antigen conjugate in admixture with a second antigen, and nor can we find any. And as Horner and Chu do not make up that deficiency of Schwartz, we are compelled to reverse the rejection.

Claims 1, 13, 14, 17, 20-23, 25-33, 37, and 40-42 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Carlson and Horner or Chu.

Chu and Horner are relied upon as above (Ans. 9).

Carlson is cited for teaching a complex comprising an ISS conjugated with an antigen such as an allergen.

According to the Examiner:

> Carlson et al. does not explicitly teach administering a second antigen with the complex. However, Carlson et al. suggests that the immunomodulatory polynucleotide be administered with at least one, or more, antigens to modulate the immune response to the antigen. [Lines 5-10, page 17, in particular] The specific immune response that Carlson et al. teaches is a Thl immune response. Therefore, administering multiple antigens with the immunomodulatory polynucleotide comprising the sequence 5'-cytosine,guanine-3' would have been prima facie obvious to one of ordinary skill in the art, at the time the invention was made. One of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation for inducing a Thl immune response to antigens administered with the immunomodulatory polynucleotide comprising the sequence 5'-cytosine,guanine-3' because Carlson et al. teaches that the immunomodulatory polynucleotide is capable of inducing a Thl immune response to antigens administered with the immunomodulatory polynucleotide.

(Ans. 8-9.)

Appellants argue that Carlson teaches a composition "comprising an immunomodulatory molecule (IMM) including an antigen, conjugated to a polynucleotide that contains or consists of at least one immunostimulatory oligonucleotide (ISS-PN)." (Carlson 1, ll. 10-13.) The portion of Carlson relied upon by the Examiner teaches:

> The oligonucleotide base of the ISS-PN/IMM conjugate is conjugated to an IMM which includes an antigen and may further include an immunomodulatory agent. An "antigen" is a substance that is recognized and bound specifically by an antibody or by a T cell antigen receptor. Antigens can include peptides, proteins, glycoproteins and polysaccharides, including portions thereof and combinations thereof. The antigens can be those found in nature or can be synthetic.

(Carlson, p. 17, ll. 5-10.)

Thus, Carlson teaches an ISS polynucleotide/antigen conjugate, but does not teach or suggest administration of ISS polynucleotide/first antigen conjugate in admixture with a second antigen. Again, the Examiner does not provide any evidence or scientific reasoning as why the ordinary artisan would have, based on the disclosure of Carlson, administer an ISS polynucleotide/first antigen conjugate in admixture with a second antigen, and nor can we find any. And, again, as Horner and Chu do not make up that deficiency of Carlson, we are compelled to reverse the rejection.

Claims 15 and 38 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Schwartz or Carlson and Horner or Chu, as further combined with Lee. In addition, claims 16 and 39 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Schwartz or Carlson and Horner or Chu, as further combined with Durali. Finally, claims 18 and 19 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Schwartz or Carlson and Horner or Chu, as further combined with Anderson.

As Lee, Durali, and Anderson do not make up the deficiencies of Schwartz or Carlson, these rejections are also reversed.

CONCLUSION

In summary, we conclude that the Examiner has not set forth a prima facie case of obviousness as to the claims on appeal, and we are thus compelled to reverse.

REVERSED

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